

What is claimed is:

- 10



wherein:

- 15

independently selected from  $\mathbb{R}^4$ ;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents independently selected from R<sup>4</sup>;

(d)  $C_3$ - $C_8$  cycloalkenyl, optionally substituted with 1-2 substituents independently selected from  $R^4$ ;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, - $NR^2$ - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from  $R^4$ ;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, - $NR^2$ - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from  $R^4$ ; or

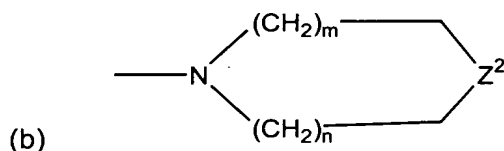
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, - $NR^2$ - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from  $R^4$ ;

$Z^1$  is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

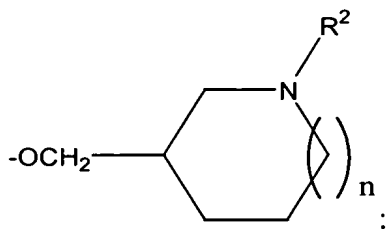
- (a)  $-NR^7R^8$ ;



wherein n is 0, 1 or 2; m is 1, 2 or 3;  $Z^2$  is -NH-, -O-, -S-, or - $CH_2$ -; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from  $R^4$ ; or

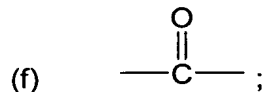
(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from  $R^4$ ; or

$Z^1$  and G in combination may be

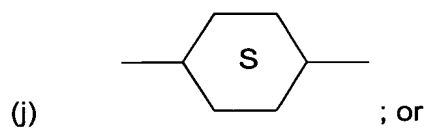


W is

- (a)  $-\text{CH}_2-$ ;
- (b)  $-\text{CH}=\text{CH}-$ ;
- (c)  $-\text{O}-$ ;
- (d)  $-\text{NR}^2-$ ;
- (e)  $-\text{S}(\text{O})_n-$ ;



- (g)  $-\text{CR}^2(\text{OH})-$ ;
- (h)  $-\text{CONR}^2-$ ;
- (i)  $-\text{NR}^2\text{CO}-$ ;



- (k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1$ - $\text{C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

- (a) hydrogen; or
- (b)  $\text{C}_1$ - $\text{C}_4$  alkyl;

$\text{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c)  $\text{C}_1$ - $\text{C}_6$  alkyl;
- (d)  $\text{C}_1$ - $\text{C}_4$  alkoxy;
- (e)  $\text{C}_1$ - $\text{C}_4$  acyloxy;
- (f)  $\text{C}_1$ - $\text{C}_4$  alkylthio;
- (g)  $\text{C}_1$ - $\text{C}_4$  alkylsulfinyl;
- (h)  $\text{C}_1$ - $\text{C}_4$  alkylsulfonyl;
- (i) hydroxy ( $\text{C}_1$ - $\text{C}_4$ )alkyl;

- (j) aryl (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (k) -CO<sub>2</sub>H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO<sub>2</sub>NHR;
- (o) -NH<sub>2</sub>;
- (p) C<sub>1</sub>-C<sub>4</sub> alkylamino;
- (q) C<sub>1</sub>-C<sub>4</sub> dialkylamino;
- (r) -NHSO<sub>2</sub>R;
- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

R<sup>5</sup> and R<sup>6</sup> are independently C<sub>1</sub>-C<sub>8</sub> alkyl or together form a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring;

R<sup>7</sup> and R<sup>8</sup> are independently

- (a) phenyl;
- (b) a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring, saturated or unsaturated;
- (c) a C<sub>3</sub>-C<sub>10</sub> heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e) C<sub>1</sub>-C<sub>6</sub> alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R<sup>5</sup> or R<sup>6</sup>;

R<sup>7</sup> and R<sup>8</sup> in either linear or ring form may optionally be substituted with up to three substituents independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R<sup>7</sup> and R<sup>8</sup> may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

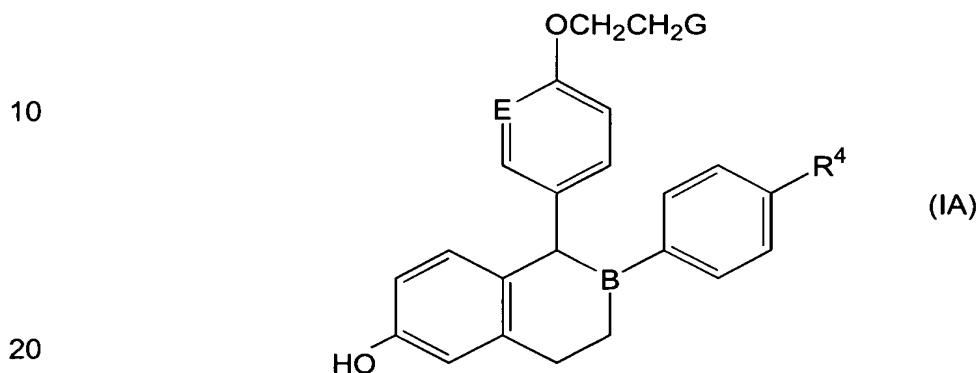
n is 0, 1 or 2;

p is 0, 1, 2 or 3;

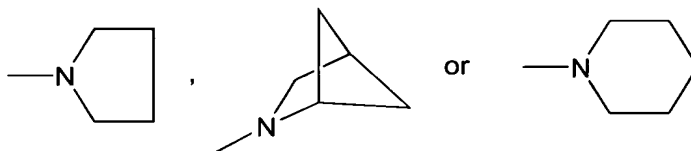
q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

3. The method of claim 1 wherein the estrogen agonist / antagonist is a compound of formula (IA)



25 wherein G is



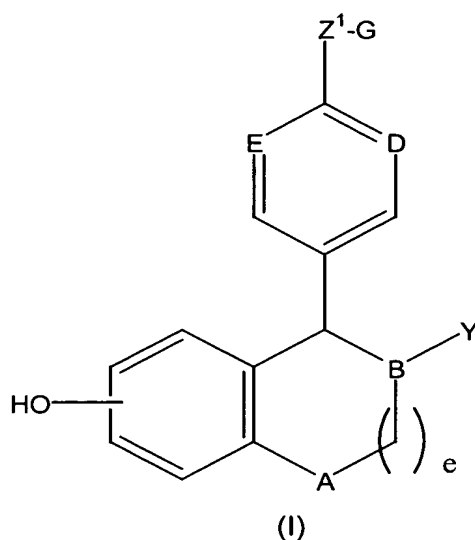
R<sup>4</sup> is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

35 4. The method of claim 1 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

40 5. The method of claim 4 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

6. A method of treating gynecomastia in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of  
45 an estrogen agonist / antagonist and testosterone.

7. The method of claim 6 wherein the estrogen agonist / antagonist is a compound of formula I



wherein:

A is selected from  $\text{CH}_2$  and  $\text{NR}$ ;

B, D and E are independently selected from  $\text{CH}$  and  $\text{N}$ ;

Y is

- (a) phenyl, optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;
- (b) naphthyl, optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;
- (c)  $\text{C}_3$ - $\text{C}_8$  cycloalkyl, optionally substituted with 1-2 substituents independently selected from  $\text{R}^4$ ;
- (d)  $\text{C}_3$ - $\text{C}_8$  cycloalkenyl, optionally substituted with 1-2 substituents independently selected from  $\text{R}^4$ ;
- (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$ , optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;
- (f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$  optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ; or

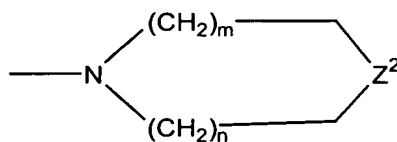
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>;

5 Z<sup>1</sup> is

- (a) -(CH<sub>2</sub>)<sub>p</sub> W(CH<sub>2</sub>)<sub>q</sub>-;
- (b) -O(CH<sub>2</sub>)<sub>p</sub> CR<sup>5</sup>R<sup>6</sup>-;
- (c) -O(CH<sub>2</sub>)<sub>p</sub> W(CH<sub>2</sub>)<sub>q</sub>-;
- (d) -OCHR<sup>2</sup>CHR<sup>3</sup>-; or
- 10 (e) -SCHR<sup>2</sup>CHR<sup>3</sup>-;

G is

- (a) -NR<sup>7</sup>R<sup>8</sup>;

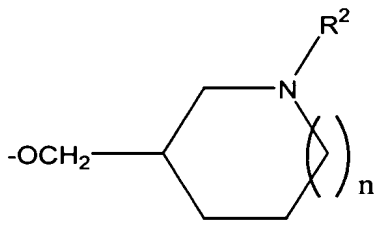


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

15 optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

(c) a bicyclic amine containing five to twelve carbon atoms,  
20 either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- 25 (a) -CH<sub>2</sub>-;
- (b) -CH=CH-;
- (c) -O-;

(d)  $-NR^2-$ ;

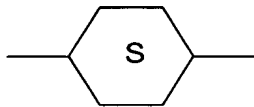
(e)  $-S(O)_n-$ ;

(f)  $\begin{array}{c} O \\ || \\ -C- \end{array}$  ;

(g)  $-CR^2(OH)-$ ;

(h)  $-CONR^2-$ ;

(i)  $-NR^2CO-$ ;

(j)  ; or

(k)  $-C\equiv C-$ ;

R is hydrogen or  $C_1-C_6$  alkyl;

$R^2$  and  $R^3$  are independently

(a) hydrogen; or

(b)  $C_1-C_4$  alkyl;

$R^4$  is

(a) hydrogen;

(b) halogen;

(c)  $C_1-C_6$  alkyl;

(d)  $C_1-C_4$  alkoxy;

(e)  $C_1-C_4$  acyloxy;

(f)  $C_1-C_4$  alkylthio;

(g)  $C_1-C_4$  alkylsulfinyl;

(h)  $C_1-C_4$  alkylsulfonyl;

(i) hydroxy ( $C_1-C_4$ )alkyl;

(j) aryl ( $C_1-C_4$ )alkyl;

(k)  $-CO_2H$ ;

(l)  $-CN$ ;

(m)  $-CONHOR$ ;

(n)  $-SO_2NHR$ ;

(o)  $-NH_2$ ;

(p)  $C_1-C_4$  alkylamino;

(q)  $C_1-C_4$  dialkylamino;

(r)  $-NHSO_2R$ ;

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- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

5 R<sup>5</sup> and R<sup>6</sup> are independently C<sub>1</sub>-C<sub>8</sub> alkyl or together form a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring;

R<sup>7</sup> and R<sup>8</sup> are independently

- (a) phenyl;
- (b) a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring, saturated or unsaturated;
- (c) a C<sub>3</sub>-C<sub>10</sub> heterocyclic ring containing up to two heteroatoms,  
10 selected from -O-, -N- and -S-;
- (d) H;
- (e) C<sub>1</sub>-C<sub>6</sub> alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R<sup>5</sup> or  
R<sup>6</sup>;

15 R<sup>7</sup> and R<sup>8</sup> in either linear or ring form may optionally be substituted with up to three substituents independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, alkoxy, hydroxy and carboxy;

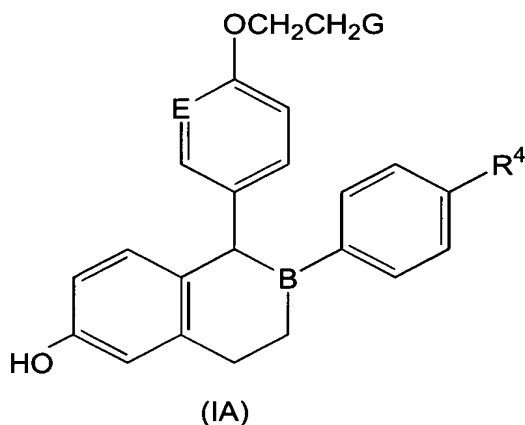
a ring formed by R<sup>7</sup> and R<sup>8</sup> may be optionally fused to a phenyl ring;

- e is 0, 1 or 2;
- 20 m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

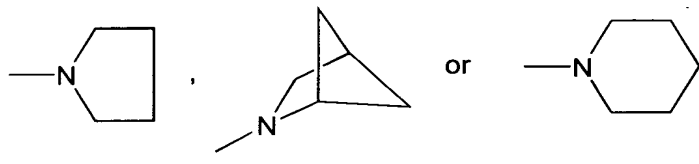
25 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

8. The method of claim 6 wherein the estrogen agonist / antagonist is a compound of formula (IA)

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wherein G is



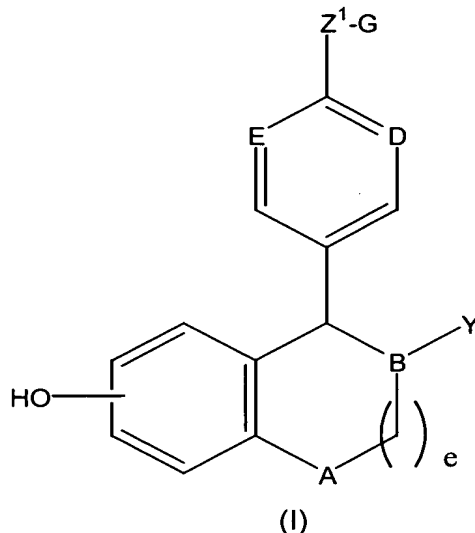
$R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

9. The method of claim 6 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

10. The method of claim 9 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

11. A method of treating lipid disorders in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

12. The method of claim 11 wherein the estrogen agonist / antagonist is a compound of formula I



wherein:

A is selected from CH<sub>2</sub> and NR;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

10 (b) naphthyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from R<sup>4</sup>;

(d) C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from R<sup>4</sup>;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally  
20 substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

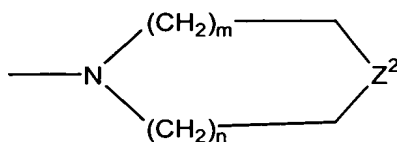
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;



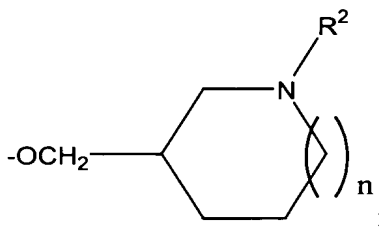
- (b)

wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

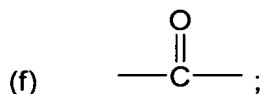
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;

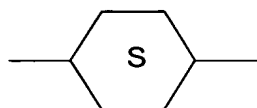


- (f)

(g)  $-\text{CR}^2(\text{OH})-$ ;

(h)  $-\text{CONR}^2-$ ;

(i)  $-\text{NR}^2\text{CO}-$ ;



(j) ; or

(k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1$ - $\text{C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

(a) hydrogen; or

(b)  $\text{C}_1$ - $\text{C}_4$  alkyl;

$\text{R}^4$  is

(a) hydrogen;

(b) halogen;

(c)  $\text{C}_1$ - $\text{C}_6$  alkyl;

(d)  $\text{C}_1$ - $\text{C}_4$  alkoxy;

(e)  $\text{C}_1$ - $\text{C}_4$  acyloxy;

(f)  $\text{C}_1$ - $\text{C}_4$  alkylthio;

(g)  $\text{C}_1$ - $\text{C}_4$  alkylsulfinyl;

(h)  $\text{C}_1$ - $\text{C}_4$  alkylsulfonyl;

(i) hydroxy ( $\text{C}_1$ - $\text{C}_4$ )alkyl;

(j) aryl ( $\text{C}_1$ - $\text{C}_4$ )alkyl;

(k)  $-\text{CO}_2\text{H}$ ;

(l)  $-\text{CN}$ ;

(m)  $-\text{CONHOR}$ ;

(n)  $-\text{SO}_2\text{NHR}$ ;

(o)  $-\text{NH}_2$ ;

(p)  $\text{C}_1$ - $\text{C}_4$  alkylamino;

(q)  $\text{C}_1$ - $\text{C}_4$  dialkylamino;

(r)  $-\text{NHSO}_2\text{R}$ ;

(s)  $-\text{NO}_2$ ;

(t) -aryl; or

(u)  $-\text{OH}$ ;

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$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

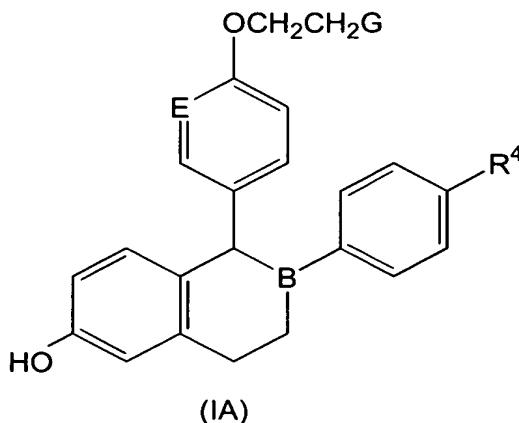
- (a) phenyl;
- 5 (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- 10 (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

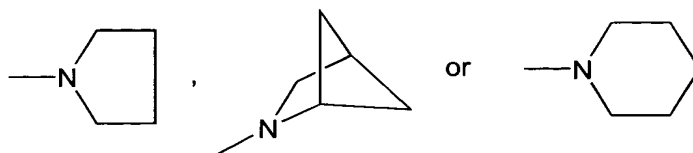
- 15 a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- 20 q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

13. The method of claim 11 wherein the estrogen agonist / antagonist is a
- 25 compound of formula (IA)

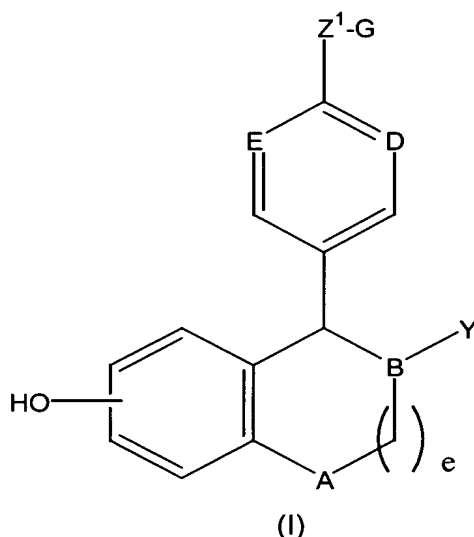


wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
14. The method of claim 11 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
- 15 15. The method of claim 14 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.
- 20 16. A method of treating cardiovascular disease in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.
- 25 17. The method of claim 16 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from CH<sub>2</sub> and NR;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

(b) naphthyl, optionally substituted with 1-3 substituents  
10 independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from R<sup>4</sup>;

(d) C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from R<sup>4</sup>;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally  
20 substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

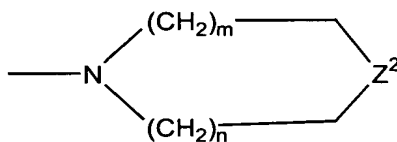


Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

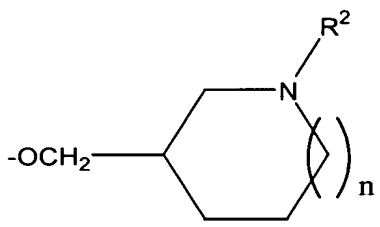


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

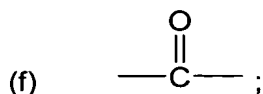
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or


Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;



- (i) 

(j)

- 5

$R^2$  and  $R^3$  are independently

- 10

- (a) hydrogen;
- (b) halogen;
- (c) C<sub>1</sub>-C<sub>6</sub> alkyl;
- (d) C<sub>1</sub>-C<sub>4</sub> alkoxy;
- (e) C<sub>1</sub>-C<sub>4</sub> acyloxy;
- (f) C<sub>1</sub>-C<sub>4</sub> alkylthio;
- (g) C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl;
- (h) C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl;
- (i) hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (j) aryl (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (k) -CO<sub>2</sub>H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO<sub>2</sub>NHR;
- (o) -NH<sub>2</sub>;
- (p) C<sub>1</sub>-C<sub>4</sub> alkylamino;
- (q) C<sub>1</sub>-C<sub>4</sub> dialkylamino;
- (r) -NHSO<sub>2</sub>R;
- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

- 15

20

25

30

$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

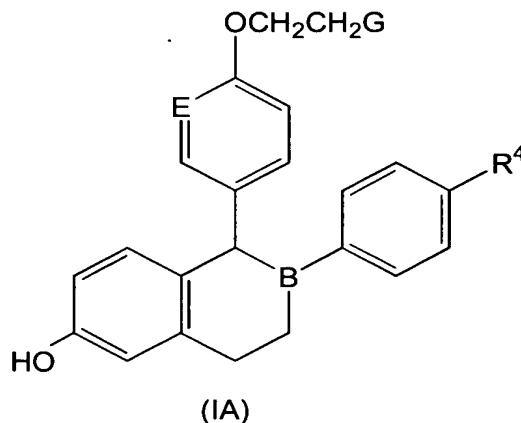
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

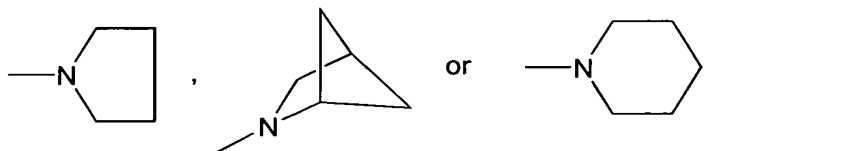
- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

- 18. The method of claim 16 wherein the estrogen agonist / antagonist is a compound of formula (IA)

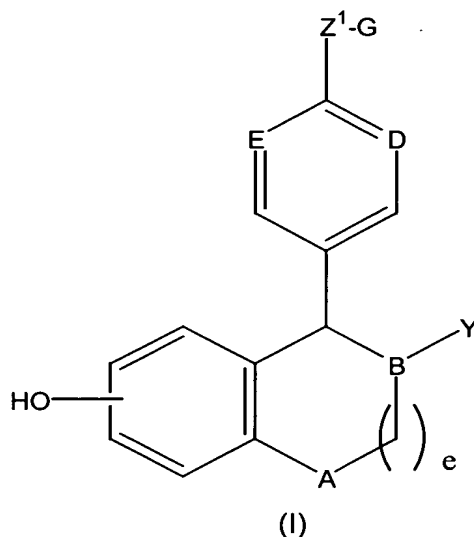


wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
- 15 19. The method of claim 16 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
- 20 20. The method of claim 19 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.
- 25 21. A method of treating atherosclerosis in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.
22. The method of claim 21 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from  $\text{CH}_2$  and  $\text{NR}$ ;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from  $\text{R}^4$ ;

10 (b) naphthyl, optionally substituted with 1-3 substituents  
independently selected from  $\text{R}^4$ ;

(c)  $\text{C}_3$ - $\text{C}_8$  cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from  $\text{R}^4$ ;

(d)  $\text{C}_3$ - $\text{C}_8$  cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from  $\text{R}^4$ ;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-,  $-\text{NR}^2$ - and  $-\text{S}(\text{O})_n$ -, optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-,  $-\text{NR}^2$ - and  $-\text{S}(\text{O})_n$ - optionally  
20 substituted with 1-3 substituents independently selected from  $\text{R}^4$ ; or

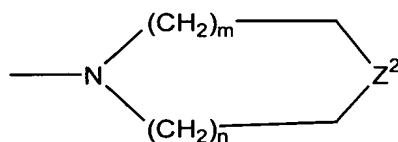
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-,  $-\text{NR}^2$ - and  $-\text{S}(\text{O})_n$ -, optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

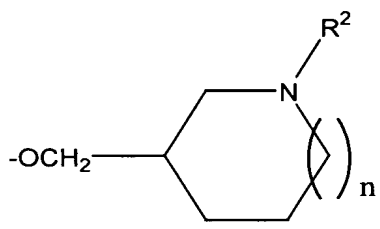


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

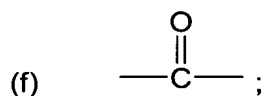
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;



(g)  $-\text{CR}^2(\text{OH})-$ ;

(h)  $-\text{CONR}^2-$ ;

(i)  $-\text{NR}^2\text{CO}-$ ;



(j) ; or

5 (k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

(a) hydrogen; or

(b)  $\text{C}_1\text{-C}_4$  alkyl;

10  $\text{R}^4$  is

(a) hydrogen;

(b) halogen;

(c)  $\text{C}_1\text{-C}_6$  alkyl;

(d)  $\text{C}_1\text{-C}_4$  alkoxy;

15 (e)  $\text{C}_1\text{-C}_4$  acyloxy;

(f)  $\text{C}_1\text{-C}_4$  alkylthio;

(g)  $\text{C}_1\text{-C}_4$  alkylsulfinyl;

(h)  $\text{C}_1\text{-C}_4$  alkylsulfonyl;

(i) hydroxy ( $\text{C}_1\text{-C}_4$ )alkyl;

20 (j) aryl ( $\text{C}_1\text{-C}_4$ )alkyl;

(k)  $-\text{CO}_2\text{H}$ ;

(l)  $-\text{CN}$ ;

(m)  $-\text{CONHOR}$ ;

(n)  $-\text{SO}_2\text{NHR}$ ;

25 (o)  $-\text{NH}_2$ ;

(p)  $\text{C}_1\text{-C}_4$  alkylamino;

(q)  $\text{C}_1\text{-C}_4$  dialkylamino;

(r)  $-\text{NHSO}_2\text{R}$ ;

(s)  $-\text{NO}_2$ ;

30 (t) -aryl; or

(u)  $-\text{OH}$ ;

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$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

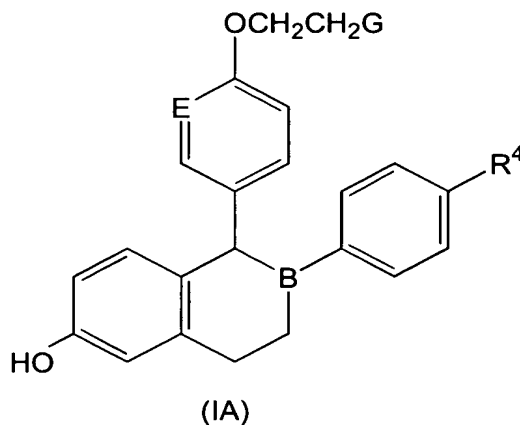
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

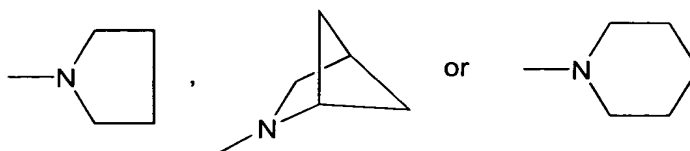
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

23. The method of claim 21 wherein the estrogen agonist / antagonist is a compound of formula (IA)





wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

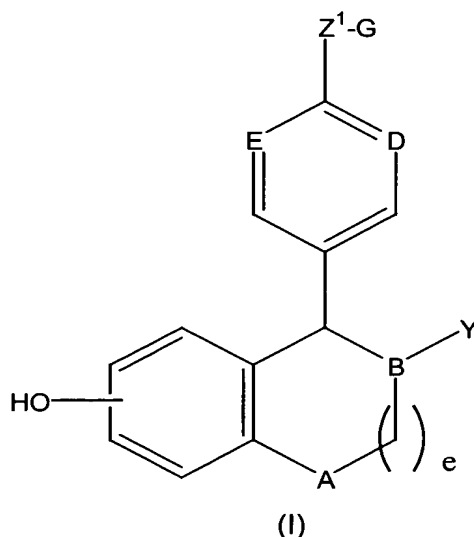
- 15 24. The method of claim 21 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 20 25. The method of claim 24 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

- 25 26. A method of maintaining or improving vascular reactivity in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

27. The method of claim 26 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from CH<sub>2</sub> and NR;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

(b) naphthyl, optionally substituted with 1-3 substituents  
10 independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from R<sup>4</sup>;

(d) C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from R<sup>4</sup>;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally  
20 substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

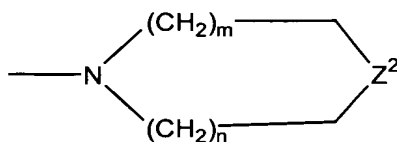
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

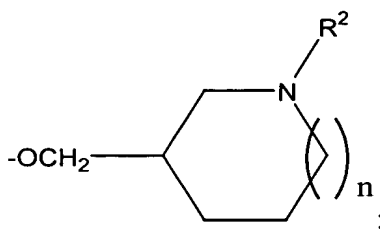


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

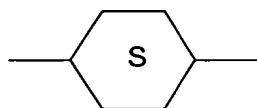
Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;
- (f)  $\begin{array}{c} O \\ || \\ -C- \end{array}$  ;

- (g)  $-\text{CR}^2(\text{OH})-$ ;
- (h)  $-\text{CONR}^2-$ ;
- (i)  $-\text{NR}^2\text{CO}-$ ;



- (j) ; or

- 5 (k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

- (a) hydrogen; or
- (b)  $\text{C}_1\text{-C}_4$  alkyl;

10  $\text{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c)  $\text{C}_1\text{-C}_6$  alkyl;
- (d)  $\text{C}_1\text{-C}_4$  alkoxy;
- 15 (e)  $\text{C}_1\text{-C}_4$  acyloxy;
- (f)  $\text{C}_1\text{-C}_4$  alkylthio;
- (g)  $\text{C}_1\text{-C}_4$  alkylsulfinyl;
- (h)  $\text{C}_1\text{-C}_4$  alkylsulfonyl;
- (i) hydroxy ( $\text{C}_1\text{-C}_4$ )alkyl;
- 20 (j) aryl ( $\text{C}_1\text{-C}_4$ )alkyl;
- (k)  $-\text{CO}_2\text{H}$ ;
- (l)  $-\text{CN}$ ;
- (m)  $-\text{CONHOR}$ ;
- (n)  $-\text{SO}_2\text{NHR}$ ;
- 25 (o)  $-\text{NH}_2$ ;
- (p)  $\text{C}_1\text{-C}_4$  alkylamino;
- (q)  $\text{C}_1\text{-C}_4$  dialkylamino;
- (r)  $-\text{NHSO}_2\text{R}$ ;
- (s)  $-\text{NO}_2$ ;
- 30 (t) -aryl; or
- (u)  $-\text{OH}$ ;

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$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

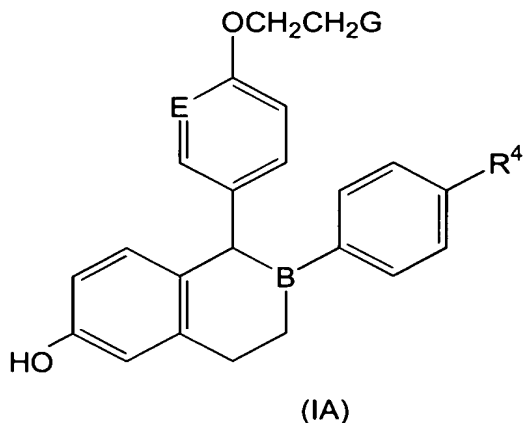
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

28. The method of claim 26 wherein the estrogen agonist / antagonist is a compound of formula (IA)



wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

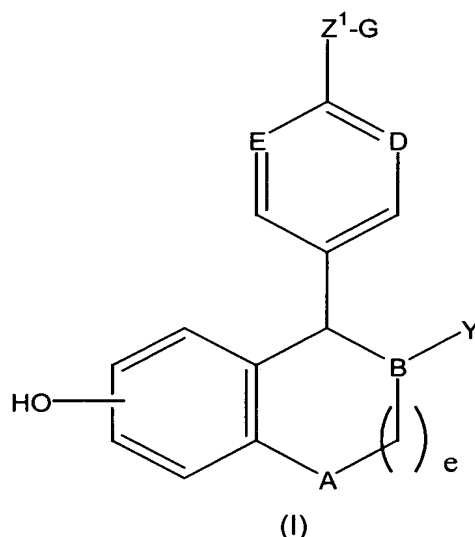
- 15 29. The method of claim 26 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 20 30. The method of claim 29 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

- 25 31. A method of increasing libido in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

32. The method of claim 31 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from  $\text{CH}_2$  and  $\text{NR}$ ;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from  $\text{R}^4$ ;

(b) naphthyl, optionally substituted with 1-3 substituents  
10 independently selected from  $\text{R}^4$ ;

(c)  $\text{C}_3\text{-C}_8$  cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from  $\text{R}^4$ ;

(d)  $\text{C}_3\text{-C}_8$  cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from  $\text{R}^4$ ;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$ , optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$  optionally  
20 substituted with 1-3 substituents independently selected from  $\text{R}^4$ ; or

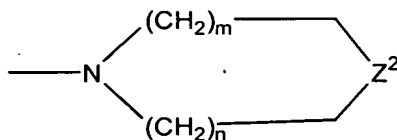
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$ , optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;



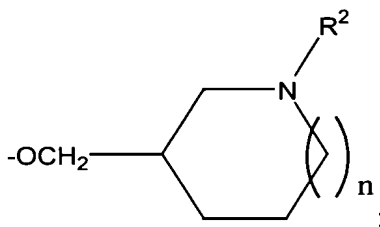
- (b)

wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

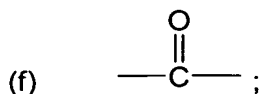
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;





- 

(k)  $\text{-C}\equiv\text{C-}$ ;

$R^2$  and  $R^3$  are independently

- $\mathbb{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c) C<sub>1</sub>-C<sub>6</sub> alkyl;
- (d) C<sub>1</sub>-C<sub>4</sub> alkoxy;
- (e) C<sub>1</sub>-C<sub>4</sub> acyloxy;
- (f) C<sub>1</sub>-C<sub>4</sub> alkylthio;
- (g) C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl;
- (h) C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl;
- (i) hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (j) aryl (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (k) -CO<sub>2</sub>H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO<sub>2</sub>NHR;
- (o) -NH<sub>2</sub>;
- (p) C<sub>1</sub>-C<sub>4</sub> alkylamino;
- (q) C<sub>1</sub>-C<sub>4</sub> dialkylamino;
- (r) -NHSO<sub>2</sub>R;
- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

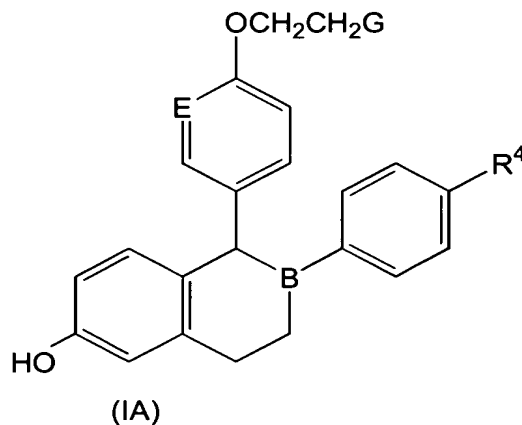
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

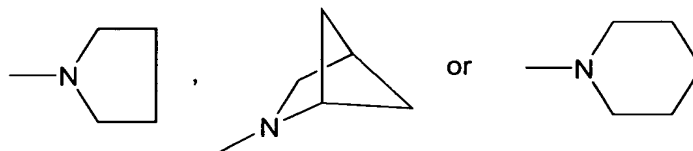
- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

33. The method of claim 31 wherein the estrogen agonist / antagonist is a compound of formula (IA)



wherein G is



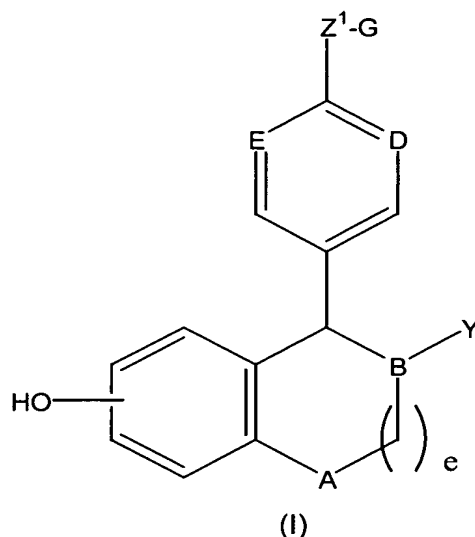
- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 15 34. The method of claim 31 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 20 35. The method of claim 34 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

- 25 36. A method of treating hypogonadism in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

37. The method of claim 36 wherein the estrogen agonist / antagonist is a compound of formula I



wherein:

A is selected from  $\text{CH}_2$  and  $\text{NR}$ ;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from  $\text{R}^4$ ;

(b) naphthyl, optionally substituted with 1-3 substituents  
10 independently selected from  $\text{R}^4$ ;

(c)  $\text{C}_3\text{-C}_8$  cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from  $\text{R}^4$ ;

(d)  $\text{C}_3\text{-C}_8$  cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from  $\text{R}^4$ ;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$ , optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$  optionally  
20 substituted with 1-3 substituents independently selected from  $\text{R}^4$ ; or

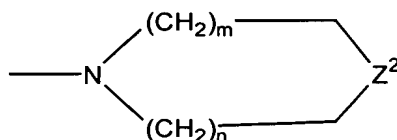
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^2-$  and  $-\text{S}(\text{O})_n-$ , optionally  
substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

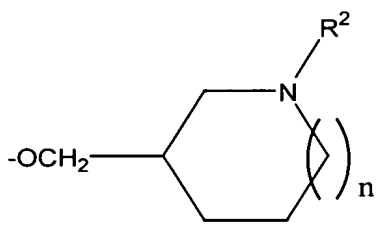


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

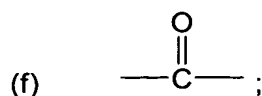
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;



- 

(k)  $-C\equiv C-$ ;

$R^2$  and  $R^3$  are independently

- $\mathbb{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c) C<sub>1</sub>-C<sub>6</sub> alkyl;
- (d) C<sub>1</sub>-C<sub>4</sub> alkoxy;
- (e) C<sub>1</sub>-C<sub>4</sub> acyloxy;
- (f) C<sub>1</sub>-C<sub>4</sub> alkylthio;
- (g) C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl;
- (h) C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl;
- (i) hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (j) aryl (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (k) -CO<sub>2</sub>H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO<sub>2</sub>NHR;
- (o) -NH<sub>2</sub>;
- (p) C<sub>1</sub>-C<sub>4</sub> alkylamino;
- (q) C<sub>1</sub>-C<sub>4</sub> dialkylamino;
- (r) -NHSO<sub>2</sub>R;
- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

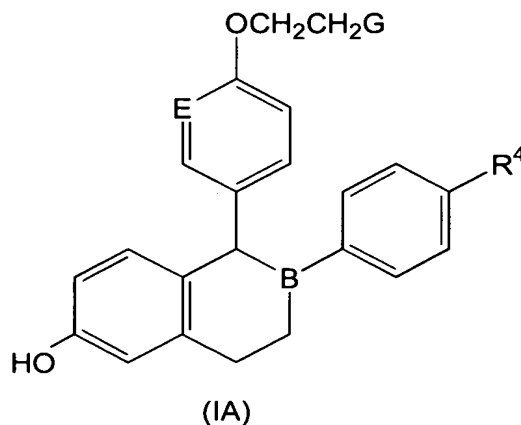
- (a) phenyl;
- 5 (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- 10 (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

- 15 a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- 20 q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

38. The method of claim 36 wherein the estrogen agonist / antagonist is a
- 25 compound of formula (IA)



wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 15 39. The method of claim 36 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

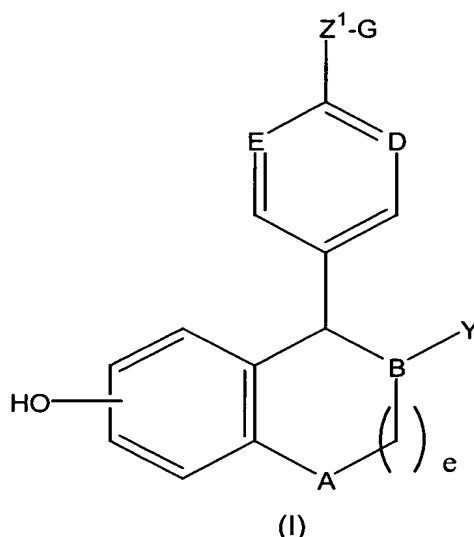
- 20 40. The method of claim 39 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

- 25 41. A method of treating benign prostatic hyperplasia in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

42. The method of claim 41 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from CH<sub>2</sub> and NR;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

(b) naphthyl, optionally substituted with 1-3 substituents  
10 independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from R<sup>4</sup>;

(d) C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from R<sup>4</sup>;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally  
20 substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

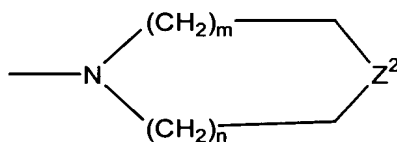
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

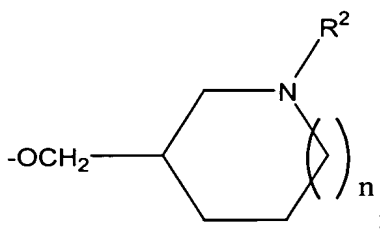


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

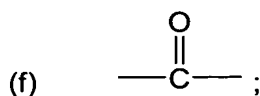
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be



W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;



- (g)  $-\text{CR}^2(\text{OH})-$ ;
- (h)  $-\text{CONR}^2-$ ;
- (i)  $-\text{NR}^2\text{CO}-$ ;



- (j) ; or
- (k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1$ - $\text{C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

- (a) hydrogen; or
- (b)  $\text{C}_1$ - $\text{C}_4$  alkyl;

$\text{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c)  $\text{C}_1$ - $\text{C}_6$  alkyl;
- (d)  $\text{C}_1$ - $\text{C}_4$  alkoxy;
- (e)  $\text{C}_1$ - $\text{C}_4$  acyloxy;
- (f)  $\text{C}_1$ - $\text{C}_4$  alkylthio;
- (g)  $\text{C}_1$ - $\text{C}_4$  alkylsulfinyl;
- (h)  $\text{C}_1$ - $\text{C}_4$  alkylsulfonyl;
- (i) hydroxy ( $\text{C}_1$ - $\text{C}_4$ )alkyl;
- (j) aryl ( $\text{C}_1$ - $\text{C}_4$ )alkyl;
- (k)  $-\text{CO}_2\text{H}$ ;
- (l)  $-\text{CN}$ ;
- (m)  $-\text{CONHOR}$ ;
- (n)  $-\text{SO}_2\text{NHR}$ ;
- (o)  $-\text{NH}_2$ ;
- (p)  $\text{C}_1$ - $\text{C}_4$  alkylamino;
- (q)  $\text{C}_1$ - $\text{C}_4$  dialkylamino;
- (r)  $-\text{NHSO}_2\text{R}$ ;
- (s)  $-\text{NO}_2$ ;
- (t) -aryl; or
- (u)  $-\text{OH}$ ;

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$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

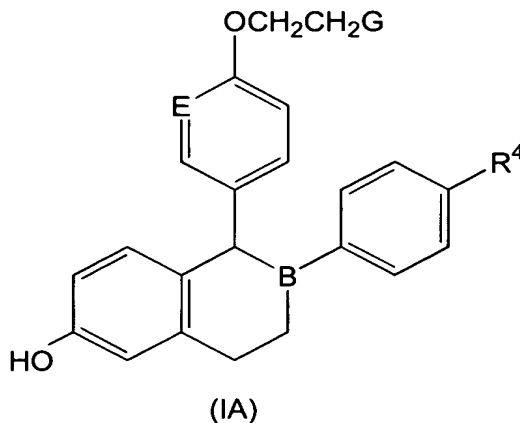
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

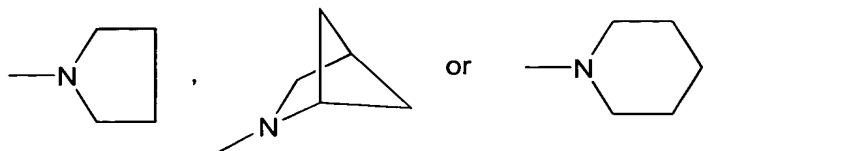
- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

43. The method of claim 41 wherein the estrogen agonist / antagonist is a compound of formula (IA)



wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

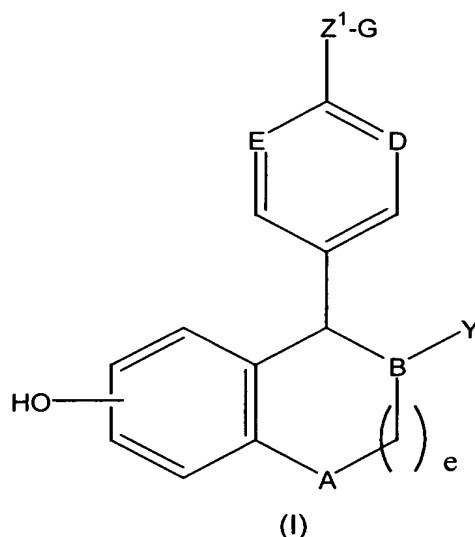
- 15 44. The method of claim 41 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 20 45. The method of claim 44 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

- 25 46. A method of treating osteoporosis in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of an estrogen agonist / antagonist and testosterone.

47. The method of claim 46 wherein the estrogen agonist / antagonist is a compound of formula I

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wherein:

A is selected from CH<sub>2</sub> and NR;

5 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

10 (b) naphthyl, optionally substituted with 1-3 substituents  
independently selected from R<sup>4</sup>;

(c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with 1-2 substituents  
independently selected from R<sup>4</sup>;

(d) C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, optionally substituted with 1-2  
substituents independently selected from R<sup>4</sup>;

15 (e) a five membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally  
20 substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

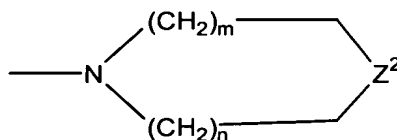
(g) a bicyclic ring system consisting of a five or six membered  
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two  
heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally  
substituted with 1-3 substituents independently selected from R<sup>4</sup>;

Z<sup>1</sup> is

- (a)  $-(CH_2)_p W(CH_2)_q-$ ;
- (b)  $-O(CH_2)_p CR^5R^6-$ ;
- (c)  $-O(CH_2)_p W(CH_2)_q-$ ;
- (d)  $-OCHR^2CHR^3-$ ; or
- (e)  $-SCHR^2CHR^3-$ ;

G is

- (a)  $-NR^7R^8$ ;

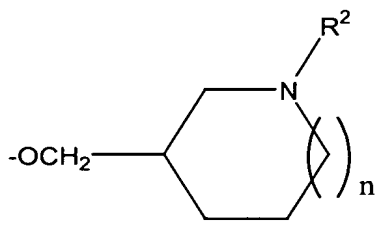


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

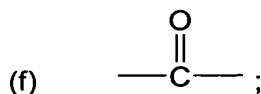
- (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

Z<sup>1</sup> and G in combination may be

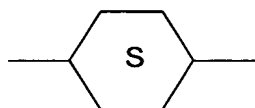


W is

- (a)  $-CH_2-$ ;
- (b)  $-CH=CH-$ ;
- (c)  $-O-$ ;
- (d)  $-NR^2-$ ;
- (e)  $-S(O)_n-$ ;



- (g)  $-\text{CR}^2(\text{OH})-$ ;
- (h)  $-\text{CONR}^2-$ ;
- (i)  $-\text{NR}^2\text{CO}-$ ;



- (j) ; or

- (k)  $-\text{C}\equiv\text{C}-$ ;

R is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

- (a) hydrogen; or
- (b)  $\text{C}_1\text{-C}_4$  alkyl;

$\text{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c)  $\text{C}_1\text{-C}_6$  alkyl;
- (d)  $\text{C}_1\text{-C}_4$  alkoxy;
- (e)  $\text{C}_1\text{-C}_4$  acyloxy;
- (f)  $\text{C}_1\text{-C}_4$  alkylthio;
- (g)  $\text{C}_1\text{-C}_4$  alkylsulfinyl;
- (h)  $\text{C}_1\text{-C}_4$  alkylsulfonyl;
- (i) hydroxy ( $\text{C}_1\text{-C}_4$ )alkyl;
- (j) aryl ( $\text{C}_1\text{-C}_4$ )alkyl;
- (k)  $-\text{CO}_2\text{H}$ ;
- (l)  $-\text{CN}$ ;
- (m)  $-\text{CONHOR}$ ;
- (n)  $-\text{SO}_2\text{NHR}$ ;
- (o)  $-\text{NH}_2$ ;
- (p)  $\text{C}_1\text{-C}_4$  alkylamino;
- (q)  $\text{C}_1\text{-C}_4$  dialkylamino;
- (r)  $-\text{NHSO}_2\text{R}$ ;
- (s)  $-\text{NO}_2$ ;
- (t) -aryl; or
- (u)  $-\text{OH}$ ;

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$R^5$  and  $R^6$  are independently  $C_1$ - $C_8$  alkyl or together form a  $C_3$ - $C_{10}$  carbocyclic ring;

$R^7$  and  $R^8$  are independently

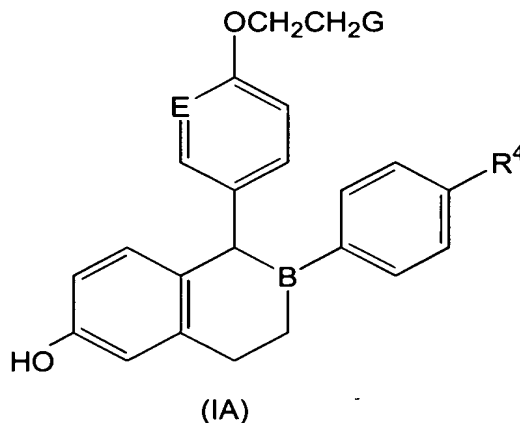
- (a) phenyl;
- (b) a  $C_3$ - $C_{10}$  carbocyclic ring, saturated or unsaturated;
- (c) a  $C_3$ - $C_{10}$  heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e)  $C_1$ - $C_6$  alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with  $R^5$  or  $R^6$ ;

$R^7$  and  $R^8$  in either linear or ring form may optionally be substituted with up to three substituents independently selected from  $C_1$ - $C_6$  alkyl, halogen, alkoxy, hydroxy and carboxy;

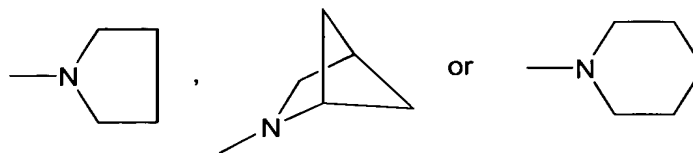
- a ring formed by  $R^7$  and  $R^8$  may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

48. The method of claim 46 wherein the estrogen agonist / antagonist is a compound of formula (IA)



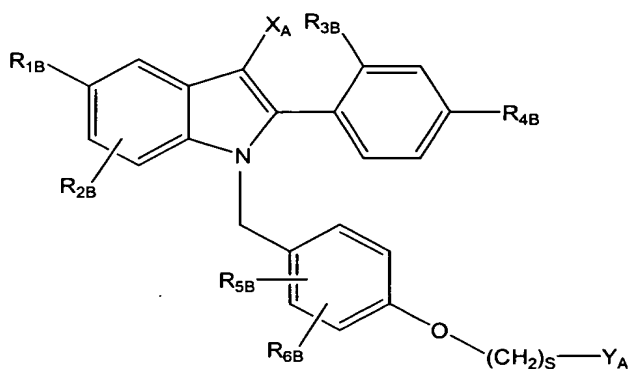
wherein G is



- 10  $R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
- 15 49. The method of claim 46 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.
- 20 50. The method of claim 49 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.
- 25 51. A method of treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient, the method comprising administering to a male patient in need thereof a therapeutically effective amount of testosterone and an estrogen agonist / antagonist that is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.
- 30 52. A method of treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient, the method comprising administering to a male patient in need thereof a

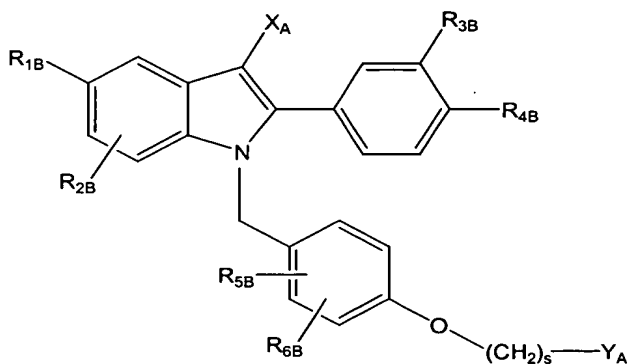
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therapeutically effective amount of testosterone and an estrogen agonist / antagonist that is selected from a compound of formulas V or VI:



5

(V)



10

(VI)

wherein:

R<sub>1B</sub> is selected from H, OH, -O-C(O)-C<sub>1</sub>-C<sub>12</sub> alkyl (straight chain or branched), -O-C<sub>1</sub>-C<sub>12</sub> alkyl (straight chain or branched or cyclic), or halogens or C<sub>1</sub>-C<sub>4</sub> halogenated ethers;

15

R<sub>2B</sub>, R<sub>3B</sub>, R<sub>4B</sub>, R<sub>5B</sub>, and R<sub>6B</sub> are independently selected from H, OH, -O-C(O)-C<sub>1</sub>-C<sub>12</sub> (straight chain or branched), -O-C<sub>1</sub>-C<sub>12</sub> (straight chain or branched or cyclic), halogens, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or branched), or trifluoromethyl;

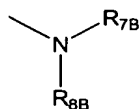
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$X_A$  is selected from H,  $C_1-C_6$  alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

5  $Y_A$  is the moiety:



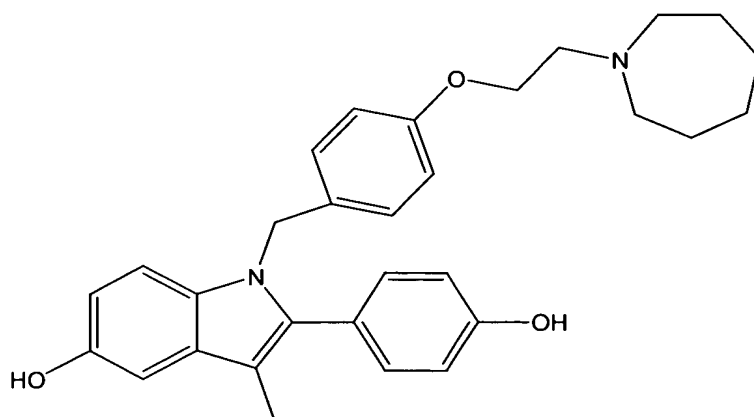
wherein:

- 10 a)  $R_{7B}$  and  $R_{8B}$  are independently selected from the group of H,  $C_1-C_6$  alkyl, or phenyl optionally substituted by CN,  $C_1-C_6$  alkyl (straight chain or branched),  $C_1-C_6$  alkoxy (straight chain or branched), halogen, -OH, -CF<sub>3</sub>, or -OCF<sub>3</sub>; or
- 15 b)  $R_{7B}$  and  $R_{8B}$  are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo,  $C_1-C_4$  alkyl, trihalomethyl,  $C_1-C_4$  alkoxy, trihalomethoxy,  $C_1-C_4$  acyloxy,  $C_1-C_4$  alkylthio,  $C_1-C_4$  alkylsulfinyl,  $C_1-C_4$  alkylsulfonyl, hydroxy ( $C_1-C_4$ )alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH( $C_1-C_4$  alkyl), -N( $C_1-C_4$  alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>,  
20 -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 ( $C_1-C_4$ )alkyl; or
- 25 c)  $R_{7B}$  and  $R_{8B}$  are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo,  $C_1-C_4$  alkyl, trihalomethyl,  $C_1-C_4$  alkoxy, trihalomethoxy,  $C_1-C_4$  acyloxy,  $C_1-C_4$  alkylthio,  $C_1-C_4$  alkylsulfinyl,  $C_1-C_4$  alkylsulfonyl, hydroxy ( $C_1-C_4$ )alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH( $C_1-C_4$  alkyl), -N( $C_1-C_4$  alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>,  
-NO<sub>2</sub>, or phenyl optionally substituted with 1-3 ( $C_1-C_4$ )alkyl; or
- 30 d)  $R_{7B}$  and  $R_{8B}$  are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo,  $C_1-C_4$  alkyl, trihalomethyl,  $C_1-C_4$  alkoxy, trihalomethoxy,  $C_1-C_4$  acyloxy,  $C_1-C_4$  alkylthio,  $C_1-C_4$  alkylsulfinyl,  $C_1-C_4$  alkylsulfonyl, hydroxy ( $C_1-C_4$ )alkyl,

-CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub> R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

e) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

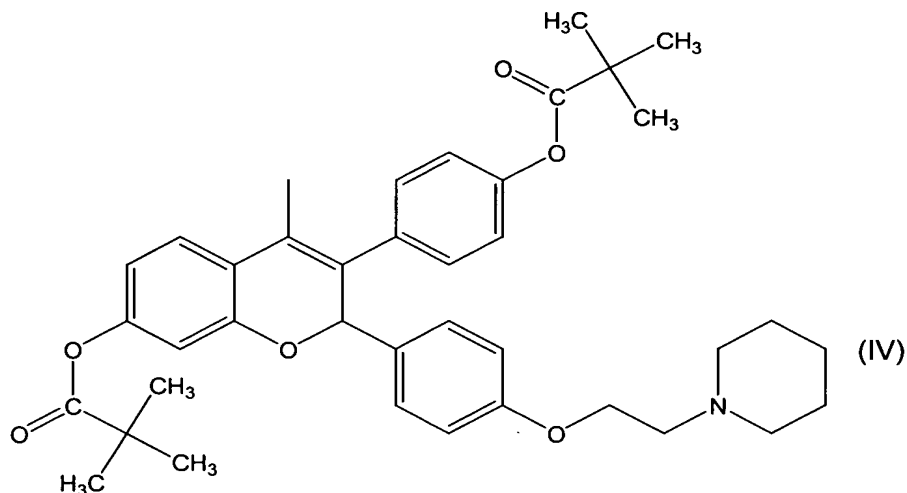
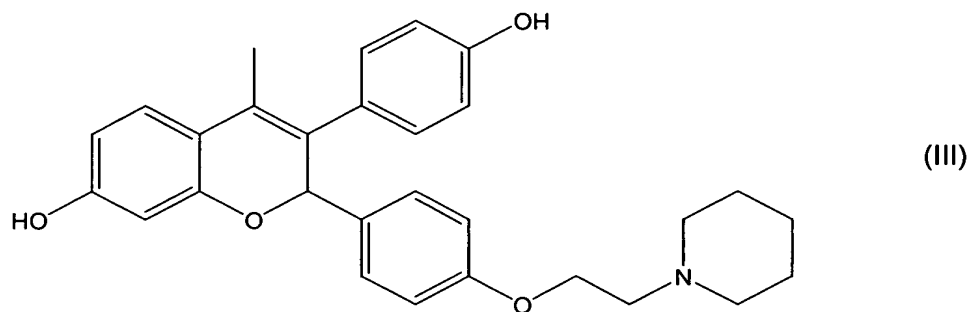
f) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub> H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>) alkyl; or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; a compound, TSE-424, of formula Va below:



(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; or

a compound of formula III or formula IV below:



25 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

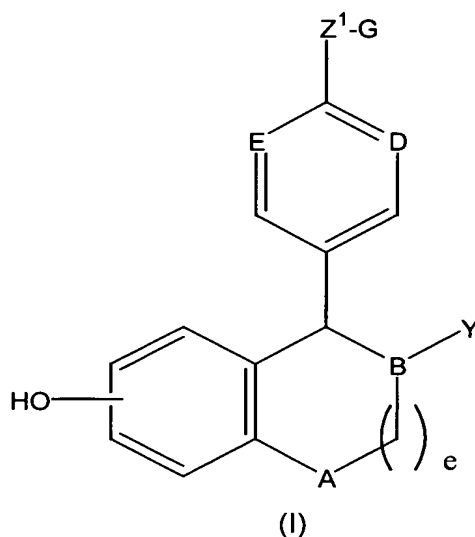
53. A kit for treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or  
30 osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient, the kit comprising:

a) one or more pharmaceutical compositions comprising an estrogen agonist / antagonist and testosterone; and

b) instructions for administering the pharmaceutical composition to treat andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increase libido, or maintain or improve vascular reactivity in a male patient.

5

54. The kit of claim 53 wherein the estrogen agonist / antagonist is a compound of formula I



10

wherein:

A is selected from  $\text{CH}_2$  and  $\text{NR}$ ;

B, D and E are independently selected from CH and N;

Y is

15

(a) phenyl, optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from  $\text{R}^4$ ;

20

(c)  $\text{C}_3\text{-C}_8$  cycloalkyl, optionally substituted with 1-2 substituents independently selected from  $\text{R}^4$ ;

(d)  $\text{C}_3\text{-C}_8$  cycloalkenyl, optionally substituted with 1-2 substituents independently selected from  $\text{R}^4$ ;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>- optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

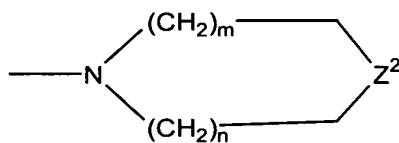
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR<sup>2</sup>- and -S(O)<sub>n</sub>-, optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>;

Z<sup>1</sup> is

- (a) -(CH<sub>2</sub>)<sub>p</sub> W(CH<sub>2</sub>)<sub>q</sub>-;
- (b) -O(CH<sub>2</sub>)<sub>p</sub> CR<sup>5</sup>R<sup>6</sup>-;
- (c) -O(CH<sub>2</sub>)<sub>p</sub>W(CH<sub>2</sub>)<sub>q</sub>-;
- (d) -OCHR<sup>2</sup>CHR<sup>3</sup>-; or
- (e) -SCHR<sup>2</sup>CHR<sup>3</sup>-;

G is

- (a) -NR<sup>7</sup>R<sup>8</sup>;



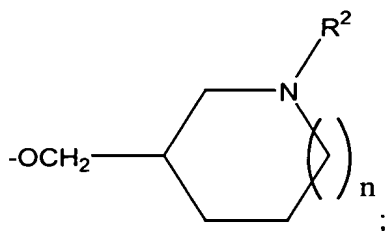
- (b)

wherein n is 0, 1 or 2; m is 1, 2 or 3; Z<sup>2</sup> is -NH-, -O-, -S-, or -CH<sub>2</sub>-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R<sup>4</sup>; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R<sup>4</sup>; or

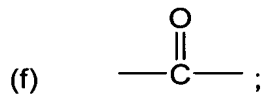
Z<sup>1</sup> and G in combination may be



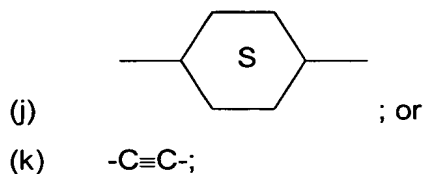


W is

- (a)  $-\text{CH}_2-$ ;
- (b)  $-\text{CH}=\text{CH}-$ ;
- (c)  $-\text{O}-$ ;
- (d)  $-\text{NR}^2-$ ;
- (e)  $-\text{S}(\text{O})_n-$ ;



- (g)  $-\text{CR}^2(\text{OH})-$ ;
- (h)  $-\text{CONR}^2-$ ;
- (i)  $-\text{NR}^2\text{CO}-$ ;



R is hydrogen or  $\text{C}_1$ - $\text{C}_6$  alkyl;

$\text{R}^2$  and  $\text{R}^3$  are independently

- (a) hydrogen; or
- (b)  $\text{C}_1$ - $\text{C}_4$  alkyl;

$\text{R}^4$  is

- (a) hydrogen;
- (b) halogen;
- (c)  $\text{C}_1$ - $\text{C}_6$  alkyl;
- (d)  $\text{C}_1$ - $\text{C}_4$  alkoxy;
- (e)  $\text{C}_1$ - $\text{C}_4$  acyloxy;
- (f)  $\text{C}_1$ - $\text{C}_4$  alkylthio;
- (g)  $\text{C}_1$ - $\text{C}_4$  alkylsulfinyl;
- (h)  $\text{C}_1$ - $\text{C}_4$  alkylsulfonyl;
- (i) hydroxy ( $\text{C}_1$ - $\text{C}_4$ )alkyl;

- (j) aryl (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- (k) -CO<sub>2</sub>H;
- (l) -CN;
- (m) -CONHOR;
- (n) -SO<sub>2</sub>NHR;
- (o) -NH<sub>2</sub>;
- (p) C<sub>1</sub>-C<sub>4</sub> alkylamino;
- (q) C<sub>1</sub>-C<sub>4</sub> dialkylamino;
- (r) -NHSO<sub>2</sub>R;
- (s) -NO<sub>2</sub>;
- (t) -aryl; or
- (u) -OH;

R<sup>5</sup> and R<sup>6</sup> are independently C<sub>1</sub>-C<sub>8</sub> alkyl or together form a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring;

R<sup>7</sup> and R<sup>8</sup> are independently

- (a) phenyl;
- (b) a C<sub>3</sub>-C<sub>10</sub> carbocyclic ring, saturated or unsaturated;
- (c) a C<sub>3</sub>-C<sub>10</sub> heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e) C<sub>1</sub>-C<sub>6</sub> alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R<sup>5</sup> or R<sup>6</sup>;

R<sup>7</sup> and R<sup>8</sup> in either linear or ring form may optionally be substituted with up to three substituents independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R<sup>7</sup> and R<sup>8</sup> may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

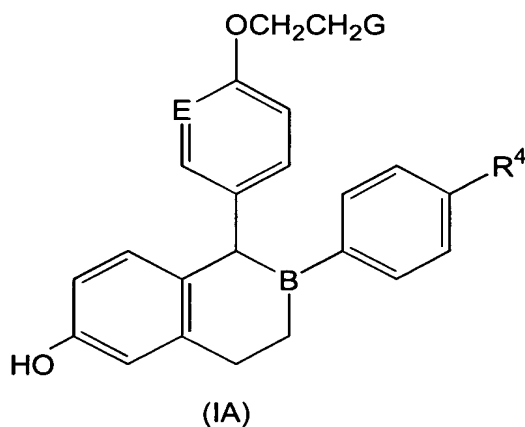
n is 0, 1 or 2;

p is 0, 1, 2 or 3;

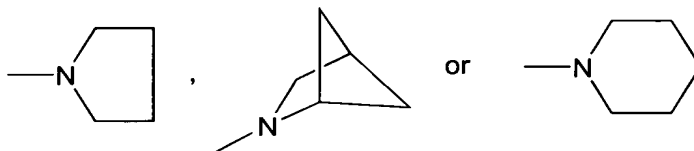
q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

55. The kit of claim 53 wherein the estrogen agonist / antagonist is a compound of formula (IA)



wherein G is



$R^4$  is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

56. The kit of claim 53 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

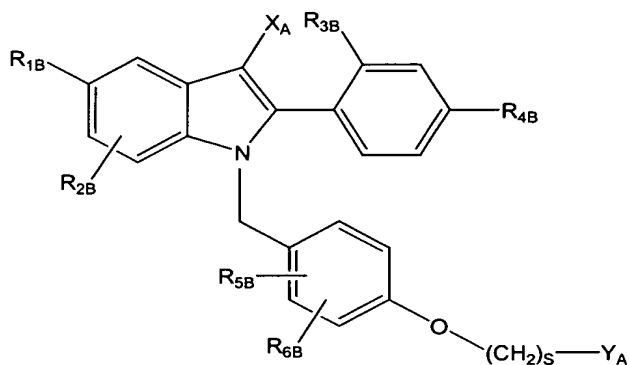
57. The kit of claim 56 wherein the estrogen agonist / antagonist is in the form of a D-tartrate salt.

58. The kit of claim 53 that includes an additional compound that is useful for treating andropause, gynecomastia, lipid disorders, cardiovascular disease,

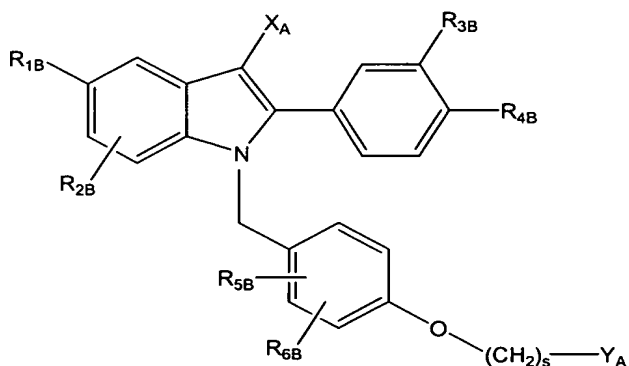
atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient.

59. A kit of claim 53 wherein the estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

60. A kit of claim 53 wherein the estrogen agonist / antagonist is selected from a compound of formulas V or VI:



(V)



(VI)

wherein:

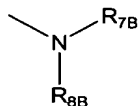
R<sub>1B</sub> is selected from H, OH, -O-C(O)-C<sub>1</sub>-C<sub>12</sub> alkyl (straight chain or branched),  
5 -O-C<sub>1</sub>-C<sub>12</sub> alkyl (straight chain or branched or cyclic), or halogens or C<sub>1</sub>-C<sub>4</sub>  
halogenated ethers;

R<sub>2B</sub>, R<sub>3B</sub>, R<sub>4B</sub>, R<sub>5B</sub>, and R<sub>6B</sub> are independently selected from H, OH, -O-C(O)-  
C<sub>1</sub>-C<sub>12</sub> (straight chain or branched), -O-C<sub>1</sub>-C<sub>12</sub> (straight chain or branched or cyclic),  
10 halogens, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or  
branched), or trifluoromethyl;

X<sub>A</sub> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, nitro, trifluoromethyl, and halogen;

15 s is 2 or 3;

Y<sub>A</sub> is the moiety:



wherein:

a) R<sub>7B</sub> and R<sub>8B</sub> are independently selected from the group of H, C<sub>1</sub>-C<sub>6</sub> alkyl, or phenyl  
optionally substituted by CN, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or branched), C<sub>1</sub>-C<sub>6</sub> alkoxy  
(straight chain or branched), halogen, -OH, -CF<sub>3</sub>, or -OCF<sub>3</sub>; or

25

b) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form a five-membered saturated heterocycle  
containing one nitrogen heteroatom, the heterocycle being optionally substituted with  
1-3 substituents independently selected from the group consisting of hydrogen,  
hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy,  
30 C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H,  
-CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>,  
-NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

c) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

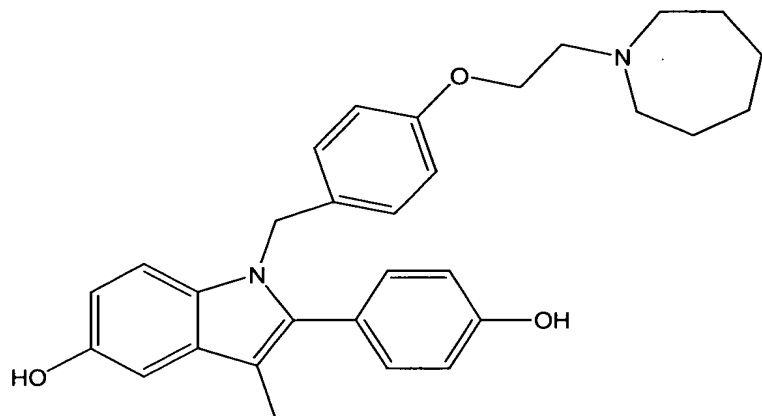
d) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

e) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

f) R<sub>7B</sub> and R<sub>8B</sub> are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub> acyloxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1B</sub>,

-NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>R<sub>1B</sub>, -NHCOR<sub>1B</sub>, -NO<sub>2</sub>, or phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>) alkyl;

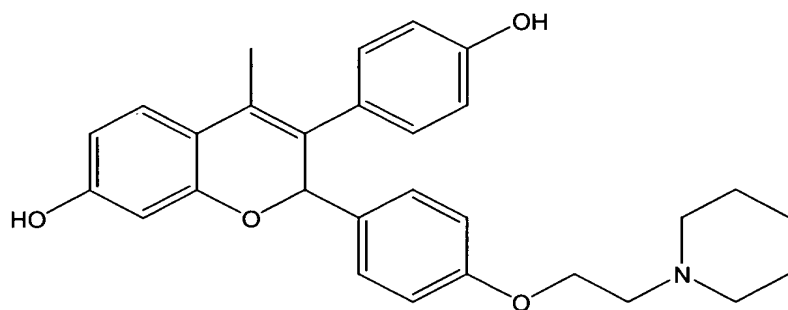
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof;  
a compound, TSE-424, of formula Va below:



5

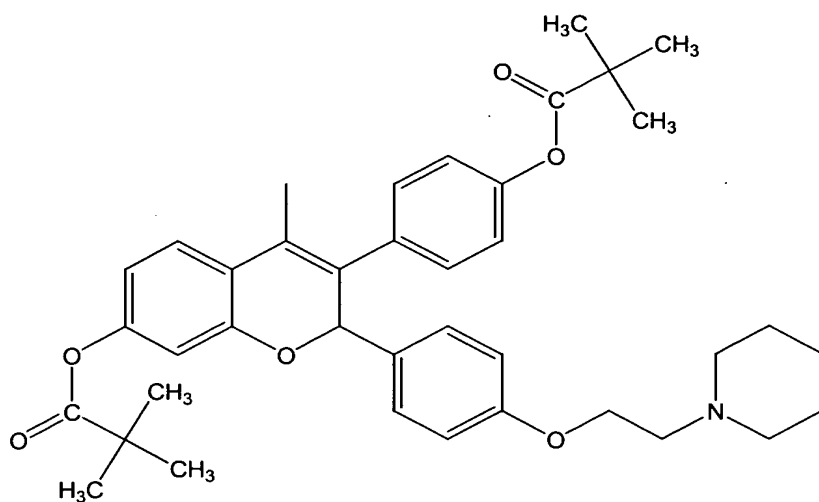
(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; or  
a compound of formula III or formula IV below:



10

(III)



(IV)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.